L5: Entry 47 of 54 File: USPT Jul 27, 1993

DOCUMENT-IDENTIFIER: US 5231170 A
TITLE: Antibodies to dense microspheres

Abstract Paragraph Left (1):
Dense microspheres can be extracted and purified to substantial homogeneity from mammalian brain tissue, and used in the screening of therapies for potential effectiveness in impeding the formation of amyloid fibrils associated with Alzheimer's disease and other forms of cerebral amyloidosis. Compounds that, at in-tissue concentrations of 10.sup.-5 M or less, inhibit amyloid formation in a test animal injected intracerebrally with dense microspheres are particularly useful in inhibiting treating cerebral amyloidosis. Antibodies to DMS (dense microspheres) are also disclosed.

Brief Summary Paragraph Right (1):
The present invention relates to the identification of compounds that act, at physiologically-compatible levels, to inhibit the formation of proteinaceous tissue deposits denoted generically as "amyloid." More specifically, the present invention relates to pharmaceutically active agents that impede formation of amyloid fibrils in vivo, and to a method for the screening of compounds which possess this activity.

Brief Summary Paragraph Right (11):
It is also an object of the present invention to provide a method of treating .beta.-amyloid diseases by the administration of a compound selected from a class of pharmaceutically active agents that have in common an ability to inhibit, at physiologically-acceptable levels, the formation of amyloid fibrils in vivo.

Brief Summary Paragraph Right (12):
It is yet another object of the present invention to provide antibodies that can be used to detect the presence of DMS in biological samples.

Brief Summary Paragraph Right (14):
In accomplishing the foregoing objects, a method has been provided, in accordance with one aspect of the present invention, for treating cerebral amyloidosis, comprising the step of administering to a subject, in whom amyloid formation is anticipated, a pharmaceutically effective amount of a compound that inhibits formation of amyloid fibrils when administered, at an in-tissue concentration of about 10.sup.-5 M or less, to a test animal that has received an intracerebral injection of DMS. In one preferred embodiment, the compound thus administered inhibits amyloid formation by acting on DMS components in such a way that a structural transition of DMS protein in situ to a .beta.-pleated sheet conformation is prevented. The method can be employed where the subject does not display clinical or other evidence indicative of Alzheimer's disease or dementia associated with another disease state, as well as when symptoms of dementia are not evident but the subject tests positive for increased risk of Alzheimer's disease or dementia due to another disease state. The method can also be administered to prevent a decline in brain function in the subject when the decline is short of dementia.

Brief Summary Paragraph Right (15):
In accordance with another aspect of the present invention, there has been provided a composition of matter consisting essentially of antibodies, preferably monoclonal antibodies, that are reactive against dense microspheres derived from mammalian brain tissue.

Brief Summary Paragraph Right (16):
A method has also been provided, in accordance with still another aspect of the present invention, for identifying individuals at risk of suffering cerebral amyloidosis, comprising the step of detecting the presence of a DMS component or an anti-DMS antibody in a biological sample of a mammalian subject, wherein the sample is not derived from brain tissue. In one preferred embodiment, the method comprises the steps of (a) providing antibodies that are reactive with a DMS component, (b) bringing the antibodies into contact with the biological sample and (c) determining whether the antibodies react with the sample. In another preferred embodiment, the method comprises (a) providing a composition comprised of a DMS component or antibody that binds an anti-DMS antibody, (b) bringing that composition into contact with the sample and (c) determining whether the composition is immunologically reactive with the sample.

Detailed Description Paragraph Right (14):
According to the present invention, an active agent that impedes in vivo formation of amyloid in DMS-injected test animals, when the agent is present at in-tissue concentrations of 10.sup.-5 M or less, is recognized to be useful in the above-mentioned method of treating cerebral amyloidosis, including Alzheimer's disease. As a further refinement, substances falling within this newly-defined category of pharmaceutically active agents--that is, the class of compounds that, at .ltoreq.10.sup.-5 M concentration levels in tissues, inhibit induced amyloid formation--can be tested, pursuant to the present invention, in a second in vivo assay.

Detailed Description Paragraph Right (15):
Particularly preferred for this purpose is the "senile animal" model for cerebral amyloidosis, where animals such as aged dogs or monkeys, which are known to develop variable numbers of Alzheimer-type cerebral senile plaques, see Wisniewski, et al., J. Neurooathol. & Exp. Neurol. 32: 566 (1973); Selkoe, et al., Science 235: 873 (1987), are tested for amyloid inhibition. This in vivo assay involves initial pretreatment- and control-biopsy monitoring to confirm and quantify the presence of senile plaque, and serial cerebral biopsy to monitor quantitatively the evolution of DMS and senile plaque in situ and the presence (or absence) of amyloid-formation inhibition.

Detailed Description Paragraph Right (16):
The method of the present invention for treating cerebral amyloidosis is used with subjects in whom amyloid formation is anticipated. The treatment can be applied, for example, to those who are at risk of developing cerebral amyloid, as in senile plaques, including the elderly, nondemented population and patients with the diagnoses listed above under the cerebral-amyloidosis rubric. In addition to its use in these patient groups, such prophylactic therapy can be effected, pursuant to the present invention, to inhibit or prevent less severe forms of brain-function decline correlated with the formation of smaller amounts of cerebral amyloid in elderly, nondemented subjects in whom dementia, due to the diseases listed above under the cerebral-amyloidosis rubric, is not expected.

Detailed Description Paragraph Right (22):
Diagnostic testing of this sort can be conducted by assaying, immunologically or otherwise, for the presence of DMS components such as DMS membrane, DMS protein or fragments thereof in biological samples not derived from brain tissue, e.g., samples of serum, spinal fluid and other bodily fluids. Testing can also be directed to detection in a subject of antibodies against one or more DMS components. In addition, prophylactic therapy according to the present invention can be administered to the nondemented population on the basis of other factors, suggesting a risk for dementia, which are revealed by radiological or diagnostic imaging, genetic testing, electroencephalography or other means.

Detailed Description Paragraph Right (33):
By means of the foregoing tests, nontoxic compounds suitable for clinical testing in human beings can be identified, pursuant to the present invention, that impede amyloid formation, preferably by inhibiting the transition of DMS protein to a .beta.-pleated sheet conformation. Because it is immunogenic in standard laboratory animals, the DMS material of the present invention can also be used to produce polyclonal and

monoclonal antibodies against dense microspheres. These antibodies, in turn, can be employed in ELISA-type assays, see, e.g., VOLLER, et al., THE ENZYME LINKED IMMUNOSORBENT ASSAY (ELISA) (Dynatech Laboratories 1979), and other immunological tests, such as radioimmunoassays, for detecting DMS in biological samples. Via conventional techniques, as described, for example, by Kennet, et al., Curr. Too. Microbiol. Immunol. 81: 77-91 (1978), anti-DMS antibodies can be produced using the DMS material of the present invention and then "tagged" with a radionuclide, a colorimetric agent or a fluorescent marker. The tagged antibodies can be used in diagnostic tests to detect the presence of components of the dense microspheres with which the antibodies react, rendering the microsphere components visualizable.

Detailed Description Paragraph Right (34):
In this context, the term "antibody" encompasses monoclonal and polyclonal antibodies. Such an antibody can belong to any antibody class (IgG, IgM, IgA, etc.). For monoclonal antibody (Mab) production, one generally proceeds by isolating lymphocytes and fusing them with myeloma cells, producing hybridomas. The cloned hybridomas are then screened for production of "anti-DMS" antibodies, i.e., antibodies that bind preferentially to a DMS component. "Antibody" also encompasses fragments, like Fab and F(ab').sub.2, of anti-DMS antibodies, and conjugates of such fragments, and so-called "antigen binding proteins" single-chain antibodies) which are based on anti-DMS antibodies, in accordance, for example, with U.S. Pat. No. 4,704,692.

Detailed Description Paragraph Right (35):
Alternatively, Mabs or a fragment thereof within the present invention can be produced using conventional procedures via the expression of isolated DNA which codes for variable regions of such an Mab in host cells like E coli. see Ward, et al., Nature 341: 544-46 (1989), or transfected murine myeloma cells, see Gillies, et al., Biotechnol. 7: 799-804 (1989), and Nakatani, et al., loc. cit., 805-10. In addition, Fab molecules can be expressed and assembled in a genetically transformed host like E. coli. A lambda vector system is available thus to express a population of Fab's with a potential diversity equal to or exceeding that of subject generating the predecessor antibody. See Huse, et al., Science 246: 1275-81 (1989).

Detailed Description Paragraph Right (36):
Antibodies against DMS components can also be employed in the generation, via conventional methodology, of anti-idiotypic antibodies (antibodies that bind an anti-DMS antibody), e.g., by the use of hybridomas as described above. See, for example, U.S. Pat. No. 4,699,880.

Detailed Description Paragraph Right (37):
The above-described materials, including DMS components, antibodies to such components, and other molecules, such as stains, that react specifically to indicate the presence of DMS components or anti-DMS antibodies, can thus be employed for the testing of DMS disruption in the brain. Such testing could be used, in accordance with the present invention, in the context of patient-population selection for therapy.

Detailed Description Paragraph Right (55):
RESULTS Standard tests for statistically significant differences of means were applied to the above-mentioned measurement data, generated from the brain sections for the six test groups (one group per tested compound) and the corresponding control groups. As shown in the following table, each of the tested compounds effected a significant reduction at 10.sup.-2 M (.rho.<0.01). But only three compound, pyrimethamine, cromolyn sodium and erythromycin, were found to inhibit amyloid formation in vivo at in-tissue levels in the range of 10.sup.-5 to 10.sup.-6 M and, hence, to fall in the category of substances suitable for the treatment method of the present invention.

Detailed Description Paragraph Right (57):
Among the compounds which were found to possess anti-amyloid activity in vitro at about 10.sup.-2 M, only those described below were determined to inhibit amyloid formation in vivo at in-tissue levels in the range of 10.sup.-5 M.

Detailed Description Paragraph Right (64):
Compounds that are structural analogues of the in vivo-active agents described above, e.g., compounds carrying one or more substituents differing from those associated with the corresponding agent, are readily prepared and routinely testable, pursuant to the

approach described herein, for in vivo efficacy in inhibiting formation of amyloid fibrils.

Detailed Description Paragraph Center (6):
EXAMPLE 2: Illustrative identification of compounds, via an in vivo assay, as effective amyloid-formation inhibitors at physiologically-compatible concentrations

Detailed Description Paragraph Center (7):
EXAMPLE 3: Further identification of compounds, via an in vivo assay, as effective amyloid-formation inhibitors at physiologically-compatible concentrations

Other Reference Publication (6):
Kipps et al. "Schemata for the Prod. of Monoclonal Antibody Producing Hybridomes" Chapter 108 handbook of Exp. Immunology pp. 108.1-108.9 Blackwell Sci. Pub. London, 1967.

CLAIMS:

1. A composition of matter consisting essentially of antibodies that specifically bind dense microspheres derived from mammalian brain tissue.

2. A composition of matter according to claim 1, wherein said antibodies are monoclonal antibodies.

L5: Entry 49 of 54 File: USPT Jun 22, 1993

DOCUMENT-IDENTIFIER: US 5221607 A
TITLE: Assays and reagents for amyloid deposition

Drawing Description Paragraph Right (2):
FIG. 2 illustrates the results of immunoprecipitation of .sup.35 S-methionine labeled VV:A99 infected CV-1 cell lysates using APCP antibodies. The arrows mark A99 protein.

Drawing Description Paragraph Right (3):
FIGS. 3A-D are fluorescent photomicrographs of infected CV-1 cells stained with APCP antibodies. FIG. 3A is a Mock control; FIG. 3B is a VV:CONT control; FIG. 3C is the VV:99 construct; and FIG. 3D is the VV:42 construct. The magnification is 200x with a 0.4 second exposure time for each photo.

Detailed Description Paragraph Right (12):
The coding sequences for the amyloid proteins can be inserted into vaccinia virus plasmid insertion vectors for the purpose of generating recombinant vaccinia viruses using the methods described in Moss et al., (1983) Methods in Gene Amplification, Vol. 3, Elsevier-North Holland, p. 202-213; and in Moss et al., (1984) J Virol 49:857:864. The amyloid-vaccinia recombinants can then be used for (1) expression of the respective amyloid protein and analysis for preamyloid formation, and (2) production of amyloid antibodies.

Detailed Description Paragraph Right (20):
The diagnosis of amyloidosis is established by demonstration of the characteristic emerald-green birefringence of tissue specimens stained with Congo red and examined by polarization microscopy. Congo red staining is generally carried out using commercially available diagnostic kits. The isolation and characterization of the A4 protein has allowed specific antibodies to be raised that recognized cerebral amyloid in Alzheimer's disease (Allsop et al(1986) Neurosci Lett 68:252-256). Moreover, Tagliavini et al., (1988) supra, have demonstrated that antibodies can be generated which detect in both Alzheimer's patients and to a lesser extent in non-demented individual's preamyloid deposits, which deposits lack the tinctorial and optical properties of amyloid and are, therefore, undetectable using conventional staining methods employing principally Congo red, but also thioflavin S or silver salts.

Detailed Description Paragraph Right (21):
Standard protocols can be employed for preparing antibodies directed against the amyloid proteins of the invention. Techniques for preparing both polyclonal and monoclonal antibodies are well known in the art. Briefly, polyclonal antibodies are prepared by injecting amyloid protein or synthetic amyloid peptides with an adjuvant into an animal such as rabbits or mice. The amyloid protein may need to be conjugated to a carrier protein such as bovine serum albumin or keyhole limpet hemacyanin using a chemical process which employs carbodiimide, glutaraldehyde, or other cross-linking agents. Alternatively, the protein may be administered without being conjugated to a carrier protein. Vaccinia virus recombinants which are expressing amyloid proteins may also be used to prepare antibodies. The vaccinia virus recombinants are injected into an animal and then the animal is boosted several weeks after the initial immunization. Ten days to two weeks later the animals are bled and antiserum is collected and analyzed for titer.

Detailed Description Paragraph Right (22):
Monoclonal antibodies are commonly prepared by fusing, under appropriate conditions,

B-lymphocytes of an animal which is making polyclonal antibodies with an immortalizing myeloma cell line. The B-lymphocytes can be spleen cells or peripheral blood lymphocytes. Techniques for fusion are also well known in the art, and in general, involve mixing the cells with a fusing agent such as polyethylene glycol. Successful hybridoma formation is assessed and selected by standard procedures such as, for example, HAT medium. From among successful hybridomas, those secreting the desired antibody are screened by assaying the culture medium for their presence.

Detailed Description Paragraph Right (23):
Standard immunological techniques such as ELISA (enzyme-linked immunoassay), RIA (radioimmunoassay), IFA (immunofluorescence assay) and Western blot analysis, which are well known in the art, can be employed for diagnostic screening for amyloid expression. A vast literature now exists with respect to various modifications of the basic assay principle, which is simply that there must be a specific association between target analyte and antibody, which association is detectable qualitatively and/or quantitatively. Fluorescent, enzymatic, or radioactive labels are generally used.

Detailed Description Paragraph Right (24):
One typical arrangement utilizes competition, between labeled antigen (e.g. amyloid protein) and the analyte, for the antibody, followed by physical separation of bound and unbound fractions. Analyte competes for the binding of the labeled antigen; hence more label will remain in the unbound fraction when larger amounts of analyte are present. In this competitive-binding type assay, the sample is incubated with a known titer of labeled amyloid protein and amyloid protein antibody. Antibody-protein complex is then separated from uncomplexed reagents using known techniques and the amount of label in the complexed material is measured, e.g. by gamma counting in the case of radioimmunoassay or photometrically in the case of enzyme immunoassay. The amount of amyloid protein in the sample, if any, is determined by comparing the measured amount of label with a standard curve.

Detailed Description Paragraph Right (25):
Other embodiments of this basic principle include use of labeled antibodies per se, sandwich assays involving a three-way complex between analyte, anti-analyte antibody, and anti-antibody wherein one of the components contains a label, and separation of bound and unbound fractions using an immunoabsorbent. Agglutination assays which result in visible precipitates are also available (Limet et al., (1982) J Clin Chem Clin Biochem 20:142-147).

Detailed Description Paragraph Right (29):
The formation of the preamyloid aggregates can be monitored by standard immunocytochemical methods using, for example, beta-amyloid primary antibodies which are detected u sing a secondary, labeled anti-antibody. If one is interested in testing whether the compound of interest can inhibit preamyloid formation, the compound is introduced to the culture medium before monitoring for preamyloid aggregation. Alternatively, the compound is introduced to the culture medium after preamyloid formation has been established and this reaction mixture is monitored to see whether the compound induces amyloid resorption.

Detailed Description Paragraph Right (30):
Potential therapeutic compounds for use in the present invention include, for example, amyloid-fibril denaturing agents such as dimethyl sulfoxide, and cytotoxic agents such as colchicine and chlorambucil. The efficacy of these agents may be monitored through observation of reduced antibody binding to the amyloid deposit. Reduction in such binding is indicative of reduced preamyloid deposition. Alternatively, preamyloid formation in the host cell may trigger other cellular events which cold be employed as markers unrelated to the etiology of Alzheimer's disease, but correlative with the presence of preamyloid deposits. For example, an increase in the level of certain enzymes, specifically proteases, may be measured in lieu of the preamyloid deposition. Typically, an increase in the concentration levels of these enzymes is observed when cultured cells are subjected to stress.

Detailed Description Paragraph Right (31):
The present invention also encompasses kits suitable for the above diagnostic or screening methods. These kits contain the appropriate reagents and are constructed by

packaging the appropriate materials, including the preamyloid protein aggregates immobilized on a solid support with labeled antibodies in suitable containers, along with any other reagents (e.g., wash solutions, enzyme substrate, anti-amyloid antibodies) or other materials required for the conduct of the assay. The reagents are usually premeasured for ease of use. An optional component of the kit is a set of instructions describing any of the available immunoassay methods. For example, a kit for a direct assay can comprise preamyloid protein aggregates immobilized on a solid immunoassay support and a container comprising labeled antibody to the amyloid protein, as well as the other reagents mentioned above.

Detailed Description Paragraph Right (42):
Characterization of the CV-1 expressed VV:A42 and VV:A99 amyloid proteins was carried out employing immunoprecipitation and polyacrylamide gel analysis of .sup.35 S-methionine-labeled infected cell protein using antibodies directed against the carboxy-terminal region of the amyloid precursor.

Detailed Description Paragraph Right (43):
The beta-amyloid antibodies were generated from synthetic peptides. The synthetic peptides were prepared using solid phase synthesis according to standard protocols. Purification of the crude peptides was accomplished by desalting with gel filtration followed by ion-exchange chromatography and preparative reverse-phase liquid chromatography. Each peptide was fully characterized by amino acid composition and sequence analysis. COOH-CORE corresponds to amino acids 653-680(DAEFRHDSGYEVHHQKLVFFAEDVGSSA) (the carboxy-terminal two amino acids were taken from the amino acid sequence of Masters et al., (1985) Proc Natl Acad Sci 82:4245-4249 and are different in the deduced translation of the A4 cDNA of Ponte et al., supra. COOH-B2 and COOH-C2 correspond to amino acids 736-751 (NGYENPTYKFFEQMQN), COOH-B3 and COOH-C3 correspond to amino acids 705-719(KKKQYTSIHHGVVEV) and COOH-C5 corresponds to amino acids 729-742(HLSKMQQNGYENPT). Reference for the numbering of peptides along the topology of the A4 precursor is from Ponte et al., supra. New Zealand white rabbits were immunized intradermally with 500 ug of peptide conjugated to keyhole limpet hemocyanin. The rabbits were first bled at 4 weeks and 1 week later the rabbits were boosted with 250 ug conjugated peptide. Subsequent bleeds were done at 3 week intervals with boosts following 1 week later. All animals were treated in accordance with institutional guidelines. Antibody titers against the appropriate peptide were determined by enzyme-linked immunosorbent assays coupled with horseradish peroxidase and found to be 7.4.times.10.sup.4, 2.7.times.10.sup.5, 1.times.10.sup.5, 9.1.times.10.sup.6, 8.2.times.10.sup.5, and 2.5.times.10.sup.5 for COOH-CORE, COOH-B2, COOH-C2, COOH-B3, COOH-C3, and COOH-C5, respectively.

Detailed Description Paragraph Right (44):
Antibodies to 9523 correspond to amino acids 673-685(AEDVGSKNGAIIG) and 9524 correspond to amino acids 701-712(LVMLKKQYTSI). Antibodies to these two peptides were generated by coinjecting New Zealand white rabbits each with 200 ug methylated bovine serum albumin (PBS) plus 200 ug of the respective synthetic peptide in PBS. Rabbits were boosted one, two and three weeks following primary inoculation with identical amounts of peptide. Serum samples were taken at week 6 and titered against APCP synthetic peptide. Titers achieved were 1.5.times.10.sup.4 for 9523 and 4.times.10.sup.5 for 9524.

Detailed Description Paragraph Right (51):
Viral infections were carried out at a moi from 5 to 20 viral plaque forming units (pfu) per cell and were harvested for staining at approximately 20 hours post infection. Slides prepared for immunocytochemistry were fixed with 4% paraformaldehyde and permeabilized with 0.2% Trtion X-100 prior to treatment with primary and rhodamine-conjugated second antibodies (Capell Labs). Briefly, after permeabilization, cells were washed with PBS containing 0.2% gelatin. 100 ul of primary amyloid antibody (diluted 1/200 with PBS plus 0.2% gelatin) was incubated on the cells at 37.degree. C. for 30 minutes. Cells were washed for 10 minutes in PBS and 0.2% gelatin, then incubated at 37.degree. C. for 20 minutes with a 1/200 dilution (in PBS and gelatin) of secondary antibody (goat-anti-rabbit) tagged with Rhodamine. Cells were washed for 10 min in PBS and gelatin, then mounted for visualization in a fluorescent microscope. Antibodies used with success included 9523, 9524, B3 and C5. CORE antibodies were not assessed. Alternatively, the slides were fixed in 4% paraformaldehyde then stained with Thioflavin S or Congo red, and conuterstained with hematoxylin according to

directions in commercial kits (Sigma).

Detailed Description Paragraph Right (53):
FIG. 3 shows fulorescent photomicrographs of CV-1 cells stained with 1/200 dilutions of the core domain antibodies 9523 antibodies. Specific and robust staining was seen in only the VV:A99 and VV:42 infected cells. VV:99 specific staining, but not VV:42 staining, was seen with the B3 antibody as would be anticipated since this region is not included in the VV:A42 construct (results not shown). Faint punctuate staining was observed for both antibodies on all cells presumably due to endogenous A4 precursor expression. The VV:A99 and VV:A42 infected cells displayed strong reactivity in the form of large deposit-like structures which are cell associated. The deposit-like structures are probably not cell debris from the viral cytopathicity since they are not seen in the VV:CONT cells and their immunoreactivity could be eliminated by preadsorption of the antisera with the synthetic peptide used to raise the serum.

Detailed Description Paragraph Right (64):
Following incubation, the culture media is removed, and the cells are prepared for preamyloid measurement as follows. The cells are fixed for immunocytochemical staining with amyloid antibodies. The primary antibodies are introduced followed by incubation with labelled, secondary anti-antibodies and the level of binding between the primary and secondary antibodies is measured using an ELISA plate reader to record the optical density of the labeled antibody. A smaller optical density reading as compared to a control sample of cells grown in the absence of the test drug is indicative of that drug's ability to inhibit amyloid deposition. This procedure may be modified to permit detection of preamyloid dissolution using a correlative enzyme marker.

Other Reference Publication (1):
Kohler et al., "Continuous Cultures of Fused Cells Secreting Antibody of Defined Specificity", Nature, vol. 256, pp. 495-497 (1975).

L6: Entry 52 of 84 File: USPT Dec 31, 1996

DOCUMENT-IDENTIFIER: US 5589154 A
TITLE: Methods for the prevention or treatment of vascular hemorrhaging and Alzheimer's disease

Drawing Description Paragraph Right (9):
The invention additionally provides a method for diagnosing the presence of amyloid plaques in an individual which comprises administering to the individual a labeled agent that specifically binds to a .beta.-amyloid peptide, in an amount sufficient to permit the detection of any of the .beta.-amyloid peptide that binds to the agent, wherein the agent is selected from the group consisting of (1) a tissue plasminogen activator analog that binds to .beta.-amyloid peptide, but does not bind to fibrin (2) an antibody, or an antibody derivative, that binds .beta.-amyloid peptide but does not bind fibrin.

Detailed Description Paragraph Right (26):
Since the administration of t-PA to dissolve clots of individuals suffering or recovering from acute cardiovascular disease occurs over a brief and discrete time period (generally ranging from a few hours to a few days), non-human origin antibodies may be used. Thus, polyclonal antibodies of non-human animals that bind to .beta.-amyloid peptides may be administered in accordance with the methods of the present invention, irrespective of any anti-idiotypic or anti-heterologous immune reaction that may occur. Suitable polyclonal antibodies may be prepared, for example, by immunizing female rabbits or castrated male sheep with 50 to 500 .mu.g of a .beta.-amyloid peptide preparation. The immunogen is preferably suspended in water and emulsified with Freund's Complete Adjuvant prior to injection. Animals may be injected in multiple intradermal sites (preferably subcapsularly) and are preferably boosted after 4 weeks with .beta.-amyloid peptide (in Freund's Incomplete Adjuvant) at one half the amount of peptide used for the initial immunization. If desired, additional boosts at monthly intervals using Freund's Complete Adjuvant may be given to obtain even higher antibody titers.

Detailed Description Paragraph Right (31):
In a highly preferred embodiment, populations of polyclonal .beta.-amyloid peptide antibodies, or species of monoclonal .beta.-amyloid peptide antibodies, are further screened to remove those antibodies that are additionally capable of specifically binding to fibrin. In the case of polyclonal sera, such removal can readily be accomplished by passing the sera through a column containing immobilized fibrin. In the case of monoclonal antibodies, such removal can be accomplished by evaluating the capacity of the molecule to bind fibrin, and then discarding those hybridomas that produce antibodies that specifically bind both .beta.-amyloid peptide and fibrin. The elimination of antibodies that bind fibrin serves to ensure that the antibodies will not disrupt the desired ability of the administered t-PA to dissolve fibrin clots.

Detailed Description Paragraph Right (57):
In a preferred method for treating hemorrhaging, the antibody and other amyloid peptide-binding agents of the present invention are provided concurrently with, or more preferably, prior to, the administration of a thrombolytic agent. Such antibody and other amyloid peptide-binding agents are preferably provided by injection, most preferably by intravenous infusion.

Detailed Description Paragraph Right (58):
Previously, despite the urgency of acute cardiovascular illness, the hemorrhaging

associated with the administration of thrombolytic agents led health providers to avoid providing such agents until the diagnosis of cardiovascular disease had been confirmed by a cardiologist. Since the present invention attenuates a possibility of hemorrhage, it (either alone, or in conjunction with the administration of the thrombolytic agent) may be provided by acute care providers (such as paramedics, emergency room attendants, etc.). Moreover, since no adverse side-effects of anti-amyloid antibodies are known, and since a delay between the administration of the antibodies and the administration of the thrombolytic agent is desirable, the anti-amyloid antibodies of the present invention are particularly suitable for administration by emergency medical personnel in the treatment of suspected or potential acute cardiovascular disorders.

L6: Entry 43 of 84 File: USPT Aug 10, 1999

DOCUMENT-IDENTIFIER: US 5935927 A
TITLE: Compositions and methods for stimulating amyloid removal in amyloidogenic diseases using advanced glycosylation endproducts

Brief Summary Paragraph Right (34):
Generally, the therapeutic methods of the present invention contemplate the inhibition of in vivo amyloid aggregation by the administration of an agent or a pharmaceutical composition containing such agent or a plurality of such agents, for the inhibition of the formation of advanced glycosylation endproducts involving any or all of the amyloid polypeptide and amyloid precursor polypeptide, and materials subject to such in vivo aggregation. Such agents comprise antagonists of advanced glycosylation, and include antibodies to AGEs, antibodies to AGE-amyloid polypeptide, in particular AGE-.beta.AP and AGE-amylin, as well as other ligands that would bind and neutralize the foregoing antigens. Suitable agents may also be selected from those agents that are reactive with an active carbonyl moiety on an early glycosylation product, and preferably are selected from aminoguanidine, a-hydrazinohistidine, analogs of aminoguanidine, and pharmaceutical compositions containing any of the foregoing, all as recited in detail herein. The invention set forth herein contemplates the discovery of additional agents that may then be used in like fashion and for like purpose.

Detailed Description Paragraph Right (20):
In one aspect, the present invention provides for therapeutic treatment for the prevention or inhibition of amyloidosis associated with diseases or disorders, e.g., neurodegenerative diseases, in particular Alzheimer's disease. In broad aspect, the therapeutic method of the invention involves administration of an agent that is capable of controlling the production, formation, or accumulation of advanced glycosylation endproducts. Such agents include, but are not limited to, antibodies against advanced glycosylation endproducts, ligands, including AGE receptors and active fragments thereof, capable of binding to and neutralizing advanced glycosylation endproducts, and compounds capable of inhibiting the formation of advanced glycosylation endproducts. In particular, the invention relates to an inhibitor of glycosylation, preferably an inhibitor of AGE formation, to the brain of a subject believed to be in need of such treatment. Such an agent is termed herein "capable of inhibiting the formation of AGEs", or alternatively an "inhibitor of AGE formation", "inhibitor of advanced glycosylation," or an "agent that inhibits advanced glycosylation."

L5: Entry 42 of 54 File: USPT Dec 23, 1997

DOCUMENT-IDENTIFIER: US 5700447 A
TITLE: Methods and materials for the diagnosis and treatment of conditions such as stroke

Brief Summary Paragraph Right (37):
Generally, the therapeutic methods of the present invention contemplate the inhibition of in vivo lipid oxidation, LDL level increases or apo B modifications, by the administration of an agent or a pharmaceutical composition containing such agent or a plurality of such agents, for the inhibition of the formation of advanced glycosylation endproducts involving any or all of the lipid and lipid-related materials subject to such in vivo oxidation. Such agents comprise antagonists of advanced glycosylation, and include antibodies to AGEs, antibodies to AGE-lipids, antibodies to AGE-LDL, antibodies to AGE-apo B, as well as other ligands that would bind and neutralize the foregoing antigens. Suitable agents may also be selected from those agents that are reactive with an active carbonyl moiety on an early glycosylation product, and preferably are selected from aminoguanidine, .alpha.-hydrazinohistidine, analogs of aminoguanidine, and pharmaceutical compositions containing any of the foregoing, all as recited in detail herein. The inventions set forth herein contemplate the discovery of additional agents that may then be used in like fashion and for like purpose.

Detailed Description Paragraph Right (15):
The agents contemplated for use in this method include materials selected from the group consisting of antibodies against advanced glycosylation endproducts, ligands, including AGE receptors and active fragments thereof, capable of binding to and neutralizing advanced glycosylation endproducts, and compounds capable of inhibiting the formation of advanced glycosylation endproducts. Suitable antibodies include polyclonal antibodies, monoclonal antibodies, chimeric antibodies, and active fragments thereof, all as discussed in detail below. These agents are administered to restore effective lipid metabolism and to correspondingly reduce lipid oxidation. The foregoing appreciates that lipid metabolism is in part controlled by the effective binding of the apolipoprotein apo B to the LDL receptor, so that any compounds or agents contemplated for use in this aspect of the invention, would be capable of interacting with the receptor binding domain of apo B to avert the formation of AGEs adjacent to or therewithin, and to render such receptor binding domain recognizable by the LDL receptor.

Detailed Description Paragraph Right (20):
Both the diagnostic and therapeutic methods of the present invention contemplate the use of agents that have an impact on the formation of AGE-lipids. Among these agents, antibodies to AGEs and other ligands may be prepared and used. These terms are defined below.

Detailed Description Paragraph Right (21):
The term "antibody" includes any immunoglobulin, including antibodies and fragments thereof that binds a specific epitope, and such general definition is intended to apply herein. The term therefore encompasses polyclonal, monoclonal and chimeric antibodies, the last mentioned described in further detail in U.S. Pat. Nos. 4,816,397 and 4,816,567.

Detailed Description Paragraph Right (22):
Also, an "antibody combining site" is that structural portion of an antibody molecule

comprised of heavy and light chain variable and hypervariable regions that specifically bind antigen. Exemplary antibodies include antibody molecules such as intact immunoglobulin molecules, substantially intact immunoglobulin molecules and those portions of an immunoglobulin molecule that contain the active binding site, including those portions known in the art as Fab, Fab', F(ab').sub.2 and F(v), which portions are preferred for use in therapeutic methods associated herein.

Detailed Description Paragraph Right (23):
Fab and F(ab').sub.2 portions of antibody molecules are prepared by the proteolytic reaction of papain and pepsin, respectively, on substantially intact antibody molecules by methods that are well-known. See for example, U.S. Pat. No. 4,342,566 to Theofilopolous et al. (The disclosures of the art cited herein are hereby incorporated by reference.) Fab' antibody molecule portions are also well-known and are produced from F(ab').sub.2 portions followed by reduction of the disulfide bonds linking the two heavy chain portions as with mercaptoethanol, and followed by alkylation of the resulting protein mercaptan with a reagent such as iodoacetamide.

Detailed Description Paragraph Right (24):
The phrase "monoclonal antibody" in its various grammatical forms refers to an antibody having only one species of antibody combining site capable of immunoreacting with a particular antigen. A monoclonal antibody thus typically displays a single binding affinity for any antigen with which it immunoreacts. An antibody may be prepared having a plurality of antibody combining sites, each immunospecific for a different antigen; e.g., a bispecific (chimeric) antibody.

Detailed Description Paragraph Right (26):
The term "AGE binding partners" is intended to extend to anti-AGE antibodies and to other cellular AGE binding proteins or receptors for AGEs, which AGEs may be found on peptides, molecules and cells.

Detailed Description Paragraph Right (31):
Additionally, the AGE-lipids may function to attract cells or other endogenous components, e.g., antibodies, which are effective in removing AGEs from the system, or which function in the removal of such compounds from the system. By providing AGE-lipids to the desired site, these cells and other components may be attracted to the area of application and induced to remove other harmful components.

Detailed Description Paragraph Right (32):
Another aspect of the present invention relates to compositions which can be in any pharmaceutically acceptable form, e.g., transdermal, oral, parenteral, topical (via the skin, inhalation, transmucosally, e.g., rectally, vaginally, buccally or sublingually) as well as other dosage forms administered by other routes of administration. Such compositions typically contain an AGE-lipid which is effective for treating the particular disease or condition, or is effective for attracting, activating or inducing the activity of cells or antibodies to the area of interest in an effort to control, reduce or eliminate the formation of lipofuscin, and other amyloid materials. The amount of the AGE-lipid present in the composition and thus the amount administered will depend upon the particular condition under treatment, as well as the age, weight, and condition of the patient.

Detailed Description Paragraph Right (33):
Also, the AGE-lipids of the present invention may be useful for the enhancement of the activity of other drugs or therapeutic agents. For example, the AGE-lipid can be coadministered or administered separately from another drug to take advantage of the lipid solubility of the preferred AGE-lipids which are useful herein. Likewise, the drugs can be used essentially simultaneously to attract cells or other biological components, e.g., antibodies, which are to be treated or are necessary or desired in the pharmacological site of activity for purposes of enhancing the activity of the AGE-lipid and/or the other drug.

Detailed Description Paragraph Right (36):
Likewise, the AGE-lipids of the present invention can be used to produce antibodies to AGE-lipids, and these antibodies can be used as described herein. For example, antibody formation can be induced by injecting a mammal with an immunogen comprised of an AGE-lipid and then collecting the serum of the mammal. Such serum will typically

contain antibodies which recognize and bind to AGE-lipids. These antibodies may be polyclonal or essentially monoclonal, and may be prepared e.g., by using an appropriate immunization protocol, such as a hyperimmunization protocol. Accordingly, appropriate fusion, plating, screening, selection and replication techniques can be utilized to obtain monoclonal antibodies which recognize specific epitopes on the particular AGE-lipid utilized.

Detailed Description Paragraph Right (37):
The AGE-lipids, antibodies and compositions can also be used in the assessment of the quality, preservation or degradation of stored foods or other biological substances. For example, the presence and concentration of advanced glycosylation endproducts can be identified. This technique is particularly useful in identifying undesirable concentrations of endproducts glycosylation endproducts that accumulate with prolonged storage.

Detailed Description Paragraph Right (38):
The AGE-lipids, antibodies and compositions can be used in the diagnosis and assessment of certain diseases. For example, the location and concentrations of advanced glycosylation endproducts in the body could be identified. This technique is particularly useful in identifying undesirable concentrations of advanced glycosylation endproducts, such as atheromatous plaques, or for the identification of complications of disease states such as diabetes mellitus.

Detailed Description Paragraph Right (43):
In a typical non-competitive assay in accordance with the present invention, AGE-lipids are solubilized in methanol and deposited on the assay plate by drying. The assay plates are then hydrated and sequentially exposed to anti-AGE primary antibodies and enzyme-conjugated second antibodies specific for the primary antibodies, with washing steps in between where appropriate. Enzyme levels are then determined by, for instance, substrate conversion protocols well known in the art, and the amount of AGEs can thus be measured by reference to a standard run in parallel.

Detailed Description Paragraph Right (51):
Many enzymes which can be used in these procedures are known and can be utilized. The preferred are peroxidase, .beta.-glucuronidase, .beta.-D-glucosidase, .beta.-D-galactosidase, urease, glucose oxidase plus peroxidase, hexokinase plus GPDase, RNAse, glucose oxidase plus alkaline phosphatase, NAD oxidoreductase plus luciferase, phosphofructokinase plus phosphoenol pyruvate carboxylase, aspartate aminotransferase plus phosphoenol pyruvate decarboxylase, and alkaline phosphatase. U.S. Pat. Nos. 3,654,090; 3,850,752; and 4,016,043 are referred to by way of example for their disclosure of alternative labeling material and methods. A particular enzymatic detecting material is anti-rabbit antibody prepared in goats and conjugated with alkaline phosphatase through an isothiocyanate.

Detailed Description Paragraph Right (52):
A number of fluorescent materials are known and can be utilized as labels. These include, for example, fluorescein, rhodamine and auramine. A particular fluorescent detecting material is anti-rabbit antibody prepared in goats and conjugated with fluorescein through an isothiocyanate.

Detailed Description Paragraph Right (53):
The AGE-lipids may be used to produce antibody(ies) to themselves which can be produced and isolated by standard methods including the well known hybridoma techniques. The antibody(ies) can be used in another species as through they were antigen(s) to raise antibody(ies). Both types of antibody(ies) can be used to determine the amount and location of the AGE-lipids in lipid masses, whether in foodstuffs, or in the mammalian body. For convenience, the antibody(ies) to the AGE-lipids will be referred to herein as Ab.sub.1 and antibody(ies) raised in another species as Ab.sub.2.

Detailed Description Paragraph Right (54):
The degree of glycosylation in lipid masses suspected of undergoing the same can be ascertained by the usual immunological procedures applicable to such determinations. A number of useful procedures are known. Three such procedures which are especially useful utilize either the AGE-lipid labeled with a detectable label, antibody Ab.sub.1

labeled with a detectable label, or antibody Ab.sub.2 labeled with a detectable label. The procedures may be summarized by the following equations wherein the asterisk indicates that the particle is labeled, and "Al " stands for the AGE-lipid:

Detailed Description Paragraph Right (55):
In each instance, the AGE-lipid substance forms complexes with one or more antibody(ies) or binding partners and one member of the complex is labeled with a detectable label. The fact that a complex has formed and, if desired, the amount thereof, can be determined by known methods applicable to the detection of labels.

Detailed Description Paragraph Right (56):
It will be seen from the above, that a characteristic property of Ab.sub.2 is that it will react with Ab.sub.1. This is because Ab.sub.1 raised in one mammalian species has been used in another species as an antigen to raise the antibody Ab.sub.2. For example, Ab.sub.1 may be raised in rabbits and Ab.sub.2 may be raised in goats using Ab, as an antigen. Ab.sub.2 therefore would be anti-rabbit antibody raised in goats.

Detailed Description Paragraph Right (59):
In a further variation, the test kit may be prepared and used for the purposes stated above, which operates according to a predetermined protocol (e.g. "competitive", "sandwich", "double antibody", etc.), and comprises:

Detailed Description Paragraph Right (67):
Various methods of treatment and use are applicable herein. One preferred use is for the treatment or removal of proteinaceous or fatty deposits such as amyloids or lipofuscin in a mammal. The AGE-lipid, an antibody to AGE-lipids, or a compound which inhibits the formation of AGE-lipids is administered to the mammal in need of such treatment in an amount effective to treat, remove or cause the removal of said lipofuscin.

Detailed Description Paragraph Right (68):
Another preferred use is for the treatment or prevention of skin disorders, e.g., wrinkling. The AGE-lipid, an antibody to AGE-lipids, or a compound which inhibits the formation of AGE-lipids can be administered to the mammal in an amount effective for the treatment or prevention of wrinkling. All forms of administration are possible, with the most preferred route of administration being topical application in a pharmaceutically acceptable dosage form.

Detailed Description Paragraph Right (98):
Lipids (PE or PC) were incubated with glucose as described above. AGE content was quantitated by ELISA using a specific anti-AGE antibody (see Makita et al., J. BIOL. CHEM. (1992), 267:5133-5138). Protein-linked AGEs were measured by competitive ELISA utilizing an AGE standard synthesized by incubation of glucose with BSA. In this ELISA, 1.0 U of AGE activity is defined as the amount of antibody-reactive material that is equivalent to 1.0 .mu.g of AGE-BSA standard. Lipid-derived AGEs were measured in a direct, non-competitive ELISA as follows. For each sample, triplicate 100 .mu.l aliquots of lipid-soluble material (dissolved in methanol) were added to round-bottom, 96 well plates and the solvent evaporated. The wells then were washed three times with PBS/0.05% Tween-20. Antiserum (final dilution 1/1000) was added, the plates were incubated for 1 hour at room temperature, and the wells washed and processed as described for the competitive ELISA. Control samples were developed with pre-immune serum in place of anti-AGE antiserum. Results were quantitated with reference to a standard curve that was obtained by assaying dilutions of AGE-BSA standard that were absorbed to plates in a concentration range from 0.3 ng/ml to 3 .mu.g/ml.

Detailed Description Paragraph Left (1):
The procedures and their application are all familiar to those skilled in the art and accordingly may be utilized within the scope of the present invention. The "competitive" procedure, Procedure A, is described in U.S. Pat. Nos. 3,654,090 and 3,850,752. Procedure C, the "sandwich" Procedure, is described in U.S. Pat. Nos. RE 31,006 and 4,016,043. Still other procedures are known such as the "Double antibody", or "DASP" procedure.

CLAIMS:

4. The method of claim 3, wherein said binding partner is selected from the group consisting of a receptor for an AGE, and an antibody reactive with or capable of binding to said AGE-lipid.

5. The method of claim 4, wherein said antibody to said AGE-lipid is selected from the group consisting of polyclonal antibodies, monoclonal antibodies, and chimeric antibodies.

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L10: Entry 4 of 33 File: USPT Jan 22, 2002

DOCUMENT-IDENTIFIER: US 6340783 B1
TITLE: Rodent models of human amyloidoses

Detailed Description Paragraph Right (26):
Proteoglycans (PGs) are complex macromolecules which interact with a variety of other proteins and influence the processing, accumulation and function of these proteins in a variety of tissues. Both heparan sulfate (Snow et al., 1988. Am. J. Path. 133:456; Snow et al., 1990. Am. J. Path. 137:1253) and dermatan sulfate proteoglycans (Snow et al., 1992. J. Histochem. Cytochem. 40:105) co-localize to sites of extracellular amyloid deposits in the brains of patients with Alzheimer's disease (AD). However, the nature of these interactions is not understood nor is it clear whether different classes of PGs interact with the major protein component found in brain amyloid deposits, a 39-43 amino acid peptide termed the beta-amyloid protein (BAP). In the present study, we examined whether specific PGs bound to the extracellular domain of the BAP (residues 1-28). Firstly, pretreatment of splenic and liver tissue sections with a synthetic peptide to BAP (1-28) produced strong immunoreactivity with BAP antibodies at tissue sites enriched in heparan sulfate proteoglycans (HSPGs). The BAP immunoreactivity was partially removed by pretreatment of the sections with nitrous acid or heparitinase, but not by chondroitinase ABC, suggesting that heparan sulfate GAG chains are involved in BAP binding. Secondly, .sup.35 S-sulfate labeled PGs derived from cultured bovine aortic endothelial cells (ECs) and smooth muscle cells (SMCs) preferentially bound to an affinity column containing BAP (1-28), whereas virtually no binding was observed to affinity columns containing residues 410-429 of the beta-amyloid precursor protein or bovine serum albumin. Characterization of BAP bound and non-bound fractions eluted with a linear salt gradient revealed strong binding by a high M.sub.r HSPG (M.sub.r.about.600,000-800,000), weak binding by two dermatan sulfate proteoglycans (DSPGs) (M.sub.r.about.120,000 and 220,000), and lack of binding by a large chondroitin sulfate proteoglycan (CSPG) of SMCs (M.sub.r.about.1-2.times.10.sup.-6). Binding of .sup.125 I-labeled HSPGs to the BAP was strongly inhibited by isolated basement membrane HSPG and to a lesser extent by heparin, but not by chondroitin-6-sulfate or unsulfated dextran sulfate. Heparitinase treated .sup.125 I-labeled HSPGs also bound to BAP (1-28) suggesting a HSPG core protein interaction. Finally, Scatchard analysis of the interaction of BAP (1-28) and high M.sub.r HSPGs isolated from ECs indicated high affinity (K_d =8.3.times.10.sup.-11 M) and low affinity (K_d =4.2.times.10.sup.-8 M) binding sites for the BAP, with approximately 1 mole of HSPG binding 1.8 moles of BAP. These results indicate that specific classes of PGs differentially bind to the extracellular domain of the BAP which may play an important role in the abnormal accumulation of this particular peptide.

Detailed Description Paragraph Right (100):
Beta-D-xylosides, which serve as an exogenous acceptor for initiation of GAG chains thereby decreasing intact PG synthesis (Johnson and Keller, 1979; Kanwar et al., 1984; Schwartz et al., 1974; Scwartz, 1977), estradiol beta-D-xyloside which primarily inhibits heparan sulfate synthesis (Lagemwa and Esko, 1991), and chlorate, an inhibitor of GAG chain sulfation (Keller et al., 1989), could be used also as potential inhibitors of Proteoglycan accumulation in .beta./A4 amyloid and other amyloidoses. Since xylosides have previously been shown to alter specific classes of PGs differently (Johnson and Keller, 1979; Kanwar et al., 1984; Schwartz et al., 1974; Scwartz, 1977), initial experiments will be designed to determine which classes of PGs are affected. In these studies, we will use P19 cells, which are embryonal carcinoma cells which upon stimulation with 0.3 .mu.m retinoic acid, differentiate primarily

into cholinergic neurons. These cells during neuronal differentiation also demonstrate marked increases in APP message and protein levels, corresponding with changes in HSPG synthesis (Snow, unpublished data). In these experiments, dose response to a range of concentrations of p-NO.sub.2 -phenyl-Beta-D-xyloside (to 5 mM), estradiol beta-D-xyloside (to 5 mM), and chlorate (to 40 mM) of incorporation of radiosulfate into GAG will first be assayed by CPC precipitation in extracts from cell layers and media of stem cells (day 0) and differentiated neurons (day 9). Altered incorporation into specific PG species will be monitored by SDS-PAGE to establish whether different levels of inhibition result in differential effects on specific PG species. Alpha-D-xyloside, which cannot serve as a false acceptor, will be used as a control for effects of xyloside not attributable to altered GAG chain initiation (Johnson and Keller, 1979). Once we determine, which PGs/GAGs are primarily affected, experiments will focus on alterations on APP metabolism and expression. APP metabolism in cell lysates and medium will be monitored by pulse labelling with .sup.35 S-methionine followed by immunoprecipitation and Western blotting by specific BAPP antibodies. We will look for alterations in the size of BAPP products (indicating altered BAPP cleavage). Changes in both PG and BAPP expression will also be monitored during P19 differentiation (days 0, 4, 9, 13) using Northern blotting and slot blotting. We will also look for the deposition of the BAP in a fibrillar form (i.e. amyloid) by staining with the amyloid specific dyes, congo red (Puchtler et al., 1962) and thioflavin S (Elghetany, 1988). In addition, we will look for amyloid fibril formation in these cultures by transmission electron microscopy as previously described (Snow et al., 1988). It is conceivable that altered PG synthesis, may cause the aberrant accumulation of the BAP peptide, which may then aggregate into a fibrillar form (Kirschner et al., 1987). These studies will determine whether xyloside or modifications thereof could be used as inhibitors of PG/GAG accumulation, and therefore potential inhibitors of amyloid accumulation, formation and/or persistence.

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Search Results - Record(s) 1 through 10 of 33 returned.

☐ 1. Document ID: US 20020019335 A1 Relevance Rank: 99

L10: Entry 1 of 33 File: PGPB Feb 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020019335
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020019335 A1

TITLE: Methods of investigating, diagnosing, and treating amyloidosis

PUBLICATION-DATE: February 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Solomon, Alan	Knoxville	TN	US	
Wall, Jonathan Stuart	Knoxville	TN	US	
Hrncic, Rudi	Knoxville	TN	US	
Schell, Maria	Knoxville	TN	US	

US-CL-CURRENT: 514/2; 800/12, 800/18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc
Image

☐ 2. Document ID: US 6100098 A Relevance Rank: 96

L10: Entry 10 of 33 File: USPT Aug 8, 2000

US-PAT-NO: 6100098
DOCUMENT-IDENTIFIER: US 6100098 A

TITLE: Anti-AGE IgG and uses thereof for the diagnosis of severe disease

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 3. Document ID: JP 2002503092 W, WO 9844955 A1, AU 9871034 A, EP 994728 A1, CN 1254294 A, NZ 337765 A Relevance Rank: 96

L10: Entry 28 of 33 File: DWPI Jan 29, 2002

DERWENT-ACC-NO: 1998-594476

15 Oct 98 no date

DERWENT-WEEK: 200211
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Preventing or inhibiting progression of Alzheimer's Disease - comprises use of recombinant DNA encoding an antibody specific for the N- or C-terminus of an amyloid-beta peptide

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Image | KWIC | Draw Desc

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☐ 4. Document ID: WO 9839653 A1, AU 9866896 A Relevance Rank: 96

L10: Entry 29 of 33 File: DWPI Sep 11, 1998

DERWENT-ACC-NO: 1998-496000
DERWENT-WEEK: 199842
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Preparation of pure proteoglycan, particularly perlecan - using molecular sieve, cation exchange, anion exchange or immobilised glycosaminoglycan chromatography

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Image | KWIC | Draw Desc

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☐ 5. Document ID: US 6340783 B1 Relevance Rank: 85

L10: Entry 4 of 33 File: USPT Jan 22, 2002

filed 10-03-98

US-PAT-NO: 6340783
DOCUMENT-IDENTIFIER: US 6340783 B1

TITLE: Rodent models of human amyloidoses

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Image | KWIC | Draw Desc

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☐ 6. Document ID: US 5958883 A Relevance Rank: 85

L10: Entry 13 of 33 File: USPT Sep 28, 1999

US-PAT-NO: 5958883
DOCUMENT-IDENTIFIER: US 5958883 A

TITLE: Animal models of human amyloidoses

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Image | KWIC | Draw Desc

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☐ 7. Document ID: US 6126918 A Relevance Rank: 83

L10: Entry 9 of 33 File: USPT Oct 3, 2000

US-PAT-NO: 6126918
DOCUMENT-IDENTIFIER: US 6126918 A

TITLE: Screening assays to identify therapeutic agents for amyloidosis

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 8. Document ID: US 5164295 A Relevance Rank: 83

L10: Entry 24 of 33 File: USPT Nov 17, 1992

US-PAT-NO: 5164295
DOCUMENT-IDENTIFIER: US 5164295 A

TITLE: Method for identifying amyloid protein-extracellular matrix protein affinity altering compounds

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 9. Document ID: US 6136548 A Relevance Rank: 83

L10: Entry 8 of 33 File: USPT Oct 24, 2000

US-PAT-NO: 6136548
DOCUMENT-IDENTIFIER: US 6136548 A

TITLE: Methods for identifying useful T-PA mutant derivatives for treatment of vascular hemorrhaging

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 10. Document ID: US 5262332 A Relevance Rank: 83

L10: Entry 21 of 33 File: USPT Nov 16, 1993

US-PAT-NO: 5262332
DOCUMENT-IDENTIFIER: US 5262332 A

TITLE: Diagnostic method for Alzheimer's disease: examination of non-neural tissue

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Search Results - Record(s) 11 through 20 of 33 returned.

☐ 11. Document ID: US 5589154 A Relevance Rank: 82

L10: Entry 20 of 33 File: USPT Dec 31, 1996

US-PAT-NO: 5589154
DOCUMENT-IDENTIFIER: US 5589154 A

TITLE: Methods for the prevention or treatment of vascular hemorrhaging and Alzheimer's disease

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 12. Document ID: US 5221607 A Relevance Rank: 82

L10: Entry 22 of 33 File: USPT Jun 22, 1993

US-PAT-NO: 5221607
DOCUMENT-IDENTIFIER: US 5221607 A

TITLE: Assays and reagents for amyloid deposition

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 13. Document ID: US 5801200 A Relevance Rank: 82

L10: Entry 17 of 33 File: USPT filed April 7'95 Sep 1, 1998

US-PAT-NO: 5801200
DOCUMENT-IDENTIFIER: US 5801200 A

TITLE: Methods and materials for the diagnosis and treatment of conditions such as stroke

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 14. Document ID: US 5700447 A Relevance Rank: 82

L10: Entry 19 of 33 File: USPT Dec 23, 1997

US-PAT-NO: 5700447
DOCUMENT-IDENTIFIER: US 5700447 A

TITLE: Methods and materials for the diagnosis and treatment of conditions such as stroke

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

☐ 15. Document ID: US 5780615 A Relevance Rank: 82

L10: Entry 18 of 33 File: USPT Jul 14, 1998

US-PAT-NO: 5780615
DOCUMENT-IDENTIFIER: US 5780615 A

TITLE: Glycosylation of lipids and lipid-containing particles and diagnostic and therapeutic methods and materials derived therefrom

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

☐ 16. Document ID: US 5869534 A Relevance Rank: 82

L10: Entry 14 of 33 File: USPT Feb 9, 1999

US-PAT-NO: 5869534
DOCUMENT-IDENTIFIER: US 5869534 A

TITLE: Glycosylation of lipids and lipid-containing particles, and diagnostic and therapeutic methods and materials derived therefrom

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

☐ 17. Document ID: US 6083713 A Relevance Rank: 82

L10: Entry 11 of 33 File: USPT Jul 4, 2000

US-PAT-NO: 6083713
DOCUMENT-IDENTIFIER: US 6083713 A

TITLE: Cloning and expression of .beta.APP-C100 receptor (C100-R)

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

☐ 18. Document ID: US 4666829 A Relevance Rank: 82

L10: Entry 25 of 33 File: USPT May 19, 1987

US-PAT-NO: 4666829
DOCUMENT-IDENTIFIER: US 4666829 A

TITLE: Polypeptide marker for Alzheimer's disease and its use for diagnosis

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 19. Document ID: US 5849560 A Relevance Rank: 82

L10: Entry 16 of 33 File: USPT Dec 15, 1998

US-PAT-NO: 5849560
DOCUMENT-IDENTIFIER: US 5849560 A

TITLE: Proteases causing degradation of amyloid .beta.-protein precursor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

☐ 20. Document ID: US 5200339 A Relevance Rank: 82

L10: Entry 23 of 33 File: USPT Apr 6, 1993

US-PAT-NO: 5200339
DOCUMENT-IDENTIFIER: US 5200339 A

TITLE: Proteases causing abnormal degradation of amyloid .beta.-protein precursor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc
Image

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Search Results - Record(s) 21 through 30 of 33 returned.

☐ 21. Document ID: US 20010051368 A1 Relevance Rank: 82

L10: Entry 2 of 33 File: PGPB Dec 13, 2001

PGPUB-DOCUMENT-NUMBER: 20010051368
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010051368 A1

TITLE: METHODS OF INHIBITING THE EFFECTS OF AMYLOIDOGENIC PROTEINS

PUBLICATION-DATE: December 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
LUNN, WILLIAM H.W.	INDIANAPOLIS	IN	US	

US-CL-CURRENT: 435/183; 435/195

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

☐ 22. Document ID: WO 200142306 A2, AU 200127256 A Relevance Rank: 82

L10: Entry 26 of 33 File: DWPI Jun 14, 2001

DERWENT-ACC-NO: 2001-381648
DERWENT-WEEK: 200140
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TITLE: Novel chimeric peptide containing N- or C-terminal end-specific B cell epitope from naturally occurring internal peptide cleavage product (such as beta amyloid peptide) of a precursor protein, joined to T cell epitope

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

☐ 23. Document ID: WO 9104339 A, AU 641434 B, AU 9064311 A, EP 493470 A1, EP 493470 A4, JP 05502368 W, US 5221607 A Relevance Rank: 82

L10: Entry 33 of 33 File: DWPI Apr 4, 1991

DERWENT-ACC-NO: 1991-117526
DERWENT-WEEK: 199116

TITLE: In vitro tissue culture-based assay for amyloid deposition - specific for Alzheimer's disease, useful for drug screening analysis

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 24. Document ID: JP 2001523093 W, WO 9846636 A2, AU 9871156 A, NO 9905062 A, EP 975753 A2, CZ 9903612 A3, BR 9808562 A, SK 9901432 A3, CN 1268973 A, HU 200003116 A2, MX 9909493 A1, NZ 500216 A, KR 2001006393 A, AU 740445 B Relevance Rank: 82

L10: Entry 27 of 33 File: DWPI Nov 20, 2001

DERWENT-ACC-NO: 1999-080736
DERWENT-WEEK: 200204

TITLE: Polynucleotide encoding beta-amyloid peptide binding protein - used to identify inhibitors of beta-amyloid peptide for treating Alzheimer's disease

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 25. Document ID: WO 9116628 A, EP 527823 A1, US 5213962 A, JP 05506990 W, EP 527823 A4, US 5427931 A Relevance Rank: 82

L10: Entry 32 of 33 File: DWPI Oct 31, 1991

DERWENT-ACC-NO: 1991-339971
DERWENT-WEEK: 200152

TITLE: Detecting circulating levels of amyloid precursor protein - for use in diagnosing neuro:degenerative conditions e.g. Alzheimer's disease and Down's syndrome

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 26. Document ID: WO 9640248 A1, AU 9662668 A Relevance Rank: 82

L10: Entry 30 of 33 File: DWPI Dec 19, 1996

DERWENT-ACC-NO: 1997-065147
DERWENT-WEEK: 199706

TITLE: Protein modification esp. of antibody, with lipid - by linking lipid via lipo-amine to carbohydrate side chain of protein, useful for therapy, drug targetting and diagnostic agents

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Image

KWIC | Draw Desc

☐ 27. Document ID: WO 9203542 A, AU 9185387 A, NO 9300483 A, EP 546084 A1, AU 643835 B, JP 06503948 W, EP 546084 A4, HU 69771 T Relevance Rank: 82

L10: Entry 31 of 33 File: DWPI Mar 5, 1992

DERWENT-ACC-NO: 1992-096886
DERWENT-WEEK: 199906

TITLE: Treatment and diagnosis of Alzheimer's disease - by reducing beta-protein precursor proteolysis near beta-protein N-terminus by administering proteolysis inhibitor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Image

KWIC | Draw Desc

☐ 28. Document ID: US 6214565 B1 Relevance Rank: 71

L10: Entry 6 of 33 File: USPT Apr 10, 2001

US-PAT-NO: 6214565
DOCUMENT-IDENTIFIER: US 6214565 B1

TITLE: Assay for disease related conformation of a protein and isolating same

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Image

KWIC | Draw Desc

☐ 29. Document ID: US 20010014455 A1 Relevance Rank: 71

L10: Entry 3 of 33 File: PGPB Aug 16, 2001

PGPUB-DOCUMENT-NUMBER: 20010014455
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010014455 A1

TITLE: Assay for disease related conformation of a protein and isolating same

PUBLICATION-DATE: August 16, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Prusiner, Stanley B.	San Francisco	CA	US	
Safar, Jiri G.	Concord	CA	US	

US-CL-CURRENT: 435/7.1; 435/68.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 30. Document ID: US 6294340 B1 Relevance Rank: 70

L10: Entry 5 of 33 File: USPT Sep 25, 2001

US-PAT-NO: 6294340
DOCUMENT-IDENTIFIER: US 6294340 B1

TITLE: Method of binding material to the .beta.-amyloid peptide

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 31. Document ID: US 5854392 A Relevance Rank: 69

L10: Entry 15 of 33 File: USPT Dec 29, 1998

US-PAT-NO: 5854392
DOCUMENT-IDENTIFIER: US 5854392 A

TITLE: .beta. APP-C100 receptor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
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☐ 32. Document ID: US 6020537 A Relevance Rank: 69

L10: Entry 12 of 33 File: USPT Feb 1, 2000

US-PAT-NO: 6020537
DOCUMENT-IDENTIFIER: US 6020537 A

TITLE: Prion protein standard and method of making same

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
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☐ 33. Document ID: US 6211428 B1 Relevance Rank: 69

L10: Entry 7 of 33 File: USPT Apr 3, 2001

US-PAT-NO: 6211428
DOCUMENT-IDENTIFIER: US 6211428 B1

TITLE: Transgenic mouse expressing a familial form of human amyloid precursor protein

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